

CLAIMS

Sub B2
1. A non-human transgenic animal having a transgene comprising a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which binds to a *tet* operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells.

2. The animal of claim 1, wherein the first polypeptide of the fusion protein binds to *tet* operator sequences in the absence but not the presence of tetracycline or a tetracycline analogue.

3. The animal of claim 2, wherein the first polypeptide is a Tet repressor.

Sub B3
4. The animal of claim 3, wherein the first polypeptide comprises an amino acid sequence shown in SEQ ID NO: 17.

5. The animal of claim 1, wherein the first polypeptide of the fusion protein binds to *tet* operator sequences in the presence but not the absence of tetracycline or a tetracycline analogue.

6. The animal of claim 5, wherein the first polypeptide is a mutated Tet repressor.

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7. The animal of claim 6, wherein the mutated Tet repressor has at least one amino acid substitution compared to a wild-type Tet repressor.

8. The animal of claim 7, wherein the mutated Tet repressor has an amino acid substitution at at least one amino acid position corresponding to an amino acid position selected from the group consisting of position 71, position 95, position 101 and position 102 of a wild-type Tn10-derived Tet repressor amino acid sequence.

9. The animal of claim 8, wherein the mutated Tet repressor comprises an amino acid sequence shown in SEQ ID NO: 19.

10. The animal of claim 1, wherein the second polypeptide comprises a transcription silencer domain of a protein selected from the group consisting of v-erbA, the Drosophila Krueppel protein, the retinoic acid receptor alpha, the thyroid hormone receptor alpha, the yeast Ssn6/Tup1 protein complex, the Drosophila protein even-skipped, SIR1, NeP1, the Drosophila dorsal protein, TSF3, SFI, the Drosophila hunchback protein, the Drosophila knirps protein, WT1, Oct-2.1, the Drosophila engrailed protein, E4BP4 and ZF5.

Sub B⁴
N. The animal of claim 1, further having a second transgene comprising a gene of interest operably linked to at least one *tet* operator sequence.

5 12. The animal of claim 1, which is a mouse.

13. The animal of claim 1, which is selected from a group consisting of a cow, a goat, a sheep and a pig.

10 14. A method for modulating transcription of the second transgene in the transgenic animal of claim 11, comprising administering tetracycline or a tetracycline analogue to the animal.

15 15. A non-human transgenic animal having a transgene comprising a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which binds to a *tet* operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells, wherein the transgene is integrated by at a predetermined location within a chromosome within cells of the animal. ✓

20 16. The animal of claim 15, wherein the first polypeptide of the fusion protein binds to *tet* operator sequences in the absence but not the presence of tetracycline or a tetracycline analogue.

25 17. The animal of claim 16, wherein the first polypeptide is a Tet repressor.

Sub B⁵
18. The animal of claim 17, wherein the first polypeptide comprises an amino acid sequence shown in SEQ ID NO: 17.

30 19. The animal of claim 17, wherein the first polypeptide of the fusion protein binds to *tet* operator sequences in the presence but not the absence of tetracycline or a tetracycline analogue.

20. The animal of claim 19, wherein the first polypeptide is a mutated Tet repressor.

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21. The animal of claim 20, wherein the mutated Tet repressor has at least one amino acid substitution compared to a wild-type Tet repressor.

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22. The animal of claim 21, wherein the mutated Tet repressor has an amino acid substitution at at least one amino acid position corresponding to an amino acid position selected from the group consisting of position 71, position 95, position 101 and position 102 of a wild-type Tn10-derived Tet repressor amino acid sequence.

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23. The animal of claim 22, wherein the mutated Tet repressor comprises an amino acid sequence shown in SEQ ID NO: 19.

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24. The animal of claim 15, wherein the second polypeptide comprises a transcription silencer domain of a protein selected from the group consisting of v-erbA, the Drosophila Krueppel protein, the retinoic acid receptor alpha, the thyroid hormone receptor alpha, the yeast Ssn6/Tup1 protein complex, the Drosophila protein even-skipped, SIR1, NeP1, the Drosophila dorsal protein, TSF3, SFI, the Drosophila hunchback protein, the Drosophila knirps protein, WT1, Oct-2.1, the Drosophila engrailed protein, E4BP4 and ZF5.

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25. The animal of claim 15, further having a second transgene comprising a gene of interest operably linked to at least one *tet* operator sequence.

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26. A method for modulating transcription of the second transgene in the transgenic animal of claim 25, comprising administering tetracycline or a tetracycline analogue to the animal.

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